REMARKS

Applicants acknowledge, with appreciation, the courtesy extended to their representatives by the Examiner during a telephone interview on November 8, 2002. Applicants make that interview of record herein. As suggested by the Examiner, applicants request amendment of the claims to recite a computer further comprising a computer program.

Applicants request reconsideration of the above-identified application in view of the foregoing amendments and the following remarks.

Claims 39, 42 and 43 were pending in the present application at the time of the Office Action. Applicants request amendment of claims 39, 42 and 43 to place them in condition for allowance and appeal. Amended claims 39, 42 and 43 are supported on page 1, lines 1-5, page 33, lines 8-10, page 35, lines 29-32 and page 26, lines 14-21 of the specification. These amendments do not constitute new matter.

Applicants have also amended the specification such that cross reference to related applications to which the present application claims priority is added just beneath the title on page 1. No new matter is introduced.

I. Claim Rejections under 35 U.S.C. § 101

The prior rejections of claims 39 and 42 under 35 U.S.C. § 101 have been withdrawn on the basis that they are now directed to statutory subject matter. However, the Examiner maintains that "the structural coordinates are nonfunctional descriptive material and do not distinguish the invention in terms of patentability"[2].

[2] August 21, 2002 final Office Action, paper number 31, page 3, lines 2-3

More particularly, the Examiner contends that "the claims recite statutory subject matter as they are directed to an article of manufacture (i.e. a computer comprising a computer screen), not because they recite an interfunctional relationship between the computer and data stored therein"[3]. Applicants disagree with these contentions, and believe that they do not apply to amended claims 39, 42 and 43.

Each of amended claims 39, 42 and 43 recites a computer comprising a program for producing a three-dimensional representation of a binding site or molecule or molecular complex. Each of amended claims 39, 42 and 43 further recites that the computer comprises a computer-readable data storage medium comprising a data storage material encoded with computer-readable data, wherein the data comprises structure coordinates. By means of the computer program, that computer reads the coordinates from memory and upon recognizing each coordinate, causes a three dimensional representation to be constructed in a proper axis system. The computer program interrelates the computer and the structure coordinates. Therefore, the software and the structure coordinates form a functional relationship with the computers recited in the amended claims.

The specification enables and describes the computers recited in the amended claims. Molecular Graphics manipulations are done with QUANTA software run on a Silicon Graphics Indigo2 computer (the specification at page 35, lines 29-32). Computer programs for visualization and molecular modeling, such as QUANTA (the specification at page 35, lines 29-32; page 26, line 14-21), Sybyl (the specification at page 26, line 14-21) are listed in the specification to enable one of

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[3] August 21, 2002 final Office Action, paper number 31, page 3, lines 4-6

ordinary skill in the art to use a computer to produce and visually inspect a three dimensional representation and to use that representation for drug design. Accordingly, amended claims 39, 42 and 43 "recite an interfunctional relationship between the computer and the data stored therein"[4] and comply with 35 U.S.C. § 101.

II. Claim Rejections under 35 U.S.C. § 102

Claims 39, 42 and 43 stand rejected under 35 U.S.C. § 102(b) as being "anticipated by" Staley, Comp. Usage Mater. Educ. Proc. Symp., 113-122 (1985), abstract only ("Staley"). The Examiner contends that "where a claim recites nonfunctional descriptive material which is not functionally related to the substrate on which it is stored, the nonfunctional descriptive material is considered, but not entitled to patentable weight"[5]. For essentially the same reasons, claims 39, 42 and 43 stand rejected under 35 U.S.C. § 102(e) as being "anticipated by" United States patent 5,581,476 ("Osslund").

As stated above, each of amended claims 39, 42 and 43 recites a computer for producing a three dimensional representation of a binding site for CD40 or molecule or molecular complex of CD40L. Each of the claimed computer comprises a computer program with instructions to produce a three dimensional representation, a computer-readable data storage medium comprising a data storage material encoded with computer-readable data, wherein the data comprises structure coordinates, and a computer screen for displaying a three dimensional representation. Contrary to the Examiner's contention that the structure coordinates constitute non-

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[4] August 21, 2002 final Office Action, paper number 31, page 3, lines 5-6

[5] August 21, 2002 final Office Action, paper number 31, page 4, lines 4-6

functional descriptive material, each of the computers of the amended claims comprises a computer program that functionally interrelates the computer and the structure coordinates (i.e., the software and the structure coordinates form a functional relationship with the computer).

Because the structure coordinates are in a functional relationship with the program and the computer, the amended claims are not anticipated by Staley or Osslund. Neither of those documents discloses a computer capable of producing any of the three dimensional representations recited in amended claims 39, 42 and 43. The Examiner contends that Staley and Osslund teach computers with memory and display screens "wherein the computer is capable of displaying a 3D representation of a molecule using crystallographic coordinates"[6], thereby anticipating claims 39, 42 and 43 since the coordinates are nonfunctional descriptive material. As discussed above, the coordinates are not nonfunctional descriptive material as recited in amended claims 39, 42 and 43. Therefore, neither Staley nor Osslund anticipates the computers recited in those claims.

III. Claim Rejections under 35 U.S.C. § 103

Claims 39, 42 and 43 stand rejected under 35 U.S.C. § 103(a) as being "unpatentable over" Staley in view of Peitsch, et al., International Immunity, 5: 233-238 (1993) ("Peitsch"). The Examiner contends that Staley teaches a computer for three dimensional display of crystal structures while Peitsch teaches a display of a three dimensional representation of amino acid residues 115 to 260 of CD40L. The Examiner also contends that since the Peitsch coordinates have been deposited in the

[6] August 21, 2002 final Office Action, paper number 31, page 4, lines 2-3 and lines 14-15

Protein Data Base, the structure is established. The Examiner further alleges that it would have been obvious to one skilled in the art at the time of the invention to display amino acid residues 115 to 260 of CD40L since the structure coordinates for CD40L were known. Applicants traverse, in view of the accompanying Declaration of Dr. Juswinder Singh under 37 C.F.R. § 1.132 (the "Singh Declaration") and the following remarks. As demonstrated in the Singh Declaration, Peitsch neither teaches nor suggests the structure coordinates of human CD40L which characterize the three dimensional representation of the binding sites or molecule or molecular complex recited in amended claims 39, 42 and 43. Accordingly, use of the Peitsch model in Staley's computer would not teach or suggest the computers of amended claims 39, 42 and 43.

The Singh Declaration presents experimental evidence obtained by comparing the Peitsch model to the crystal structure disclosed in the above-identified application which serves as the source for the structure coordinates recited in amended claims 39, 42 and 43. That evidence shows that the Peitsch model is not an accurate model for the structure of human CD40L. A backbone alignment between the structure of the binding site residues recited in amended claim 43 and the Peitsch model shows a root mean square deviation (rmsd) value of 2.8 Å (Singh Declaration, paragraph 10, lines 4-14). A backbone alignment between the structure of the entire CD40L crystal model of this application, as recited in claim 42, and the Peitsch model shows a root mean square deviation (rmsd) value of 2.88 Å (Singh Declaration, Figure 2 and paragraph 10, lines 15-18 and 22-25). An alignment between backbone atoms of residues Lys143, Tyr145, Arg203 and Arg207 of the crystal structure characterizing the three dimensional representation of a binding site of amended claim 39 and the

corresponding amino acid residues of the Peitsch model gives an rmsd value of 1.306 Å (Singh Declaration, paragraph 10, lines 15-22 and 25-28). These high rmsd values[7] show that the Peitsch model is not an accurate and true model of human CD40L and, therefore, does not render obvious the structure coordinates recited in the amended claims.

Although Peitsch's model for amino acid residues 115 to 260 of CD40L has been deposited in the Protein Data Bank, that model was not generated by X-ray crystallography or NMR. Instead, Peitsch relates to a three dimensional model of mouse CD40L which was derived from molecular modeling and energy minimization based on the known crystal structure of human tumor necrosis factor α (TNFα). Mouse CD40L is only about 20-25% identical with human and mouse TNFα (23.2% and 25.7 %, respectively) (Peitsch at page 233, right column, first full paragraph, lines 13-14). Because Peitsch's mouse CD40L model is derived from human TNFα, with which it has little sequence similarity (Singh Declaration, paragraph 5, lines 2-4), that model is speculative, at best (Singh Declaration, paragraph 5, lines 4-7).

Moreover, the structure disclosed in this application is the structure of human CD40L (Singh Declaration, paragraph 6, lines 1-2 and the specification at page 1, lines 1-5). The human and mouse CD40L proteins share 78% homology (Singh Declaration, paragraph 6, lines 2-5). More importantly, the amino acid sequence of residues 115 to 260 of human CD40L which encompasses the binding site residues of

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[7] These rmsd values are above the rmsd cutoff value of 1.0 Å that the present application preferably requires of identical structures (see the specification, page 13, lines 16-23).

amended claim 43 for CD40 in human CD40L differ from the corresponding mouse CD40L residues (Singh Declaration, Figure 1 and paragraph 6, lines 5-9). For all these reasons, the Peitsch model must be recognized as a speculative model of mouse CD40L (Singh Declaration, paragraph 5, lines 4-7).

For the foregoing reasons, one of skill in the art would view the Peitsch model as no more than a speculative model for the structure of human CD40L. The experimental evidence provided by the Singh Declaration makes it clear that the Peitsch model is not an accurate model of human CD40L (Singh Declaration, paragraph 6, lines 9-10 and paragraph 7, lines 1-3) and is therefore unsuitable for the structure-based drug design for agonists or antagonists of human CD40L (Singh Declaration, paragraph 7, lines 1-5) achieved by computers of amended claims 39, 42 and 43.

Because Peitsch can not provide an accurate three dimensional representation of the binding site or molecule or molecular complex recited in amended claims 39, 42 and 43, Staley, viewed in combination with Peitsch, neither teaches nor discloses the computers of amended claims 39, 42 and 43.

Applicants request the Examiner consider and enter the foregoing amendments and pass this application to issue.

Respectfully submitted,

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Appendix A

39. (Thrice Amended) A computer for producing a three dimensional representation of a binding site for CD40 defined by structure coordinates of human CD40 ligand amino acids Lys143, Arg203, Arg207 and Tyr145, which correspond to residues 28, 88, 92 and 30, respectively, of SEQ ID NO: 3, according to Table 1;

wherein said computer comprises:

(a) a computer program with instructions to produce said three dimensional representation;

(b) a computer-readable data storage medium comprising a data storage material encoded with computer-readable data, wherein said data comprises the structure coordinates of human CD40 ligand amino acids Lys143, Arg203, Arg207 and Tyr145, which correspond to residues 28, 88, 92 and 30, respectively, of SEQ ID NO: 3, according to Table 1; and

[(b)] (c) a computer screen for displaying said three dimensional representation.

42. (Twice Amended) A computer for producing a three dimensional representation of a molecule or a molecular complex defined by the structure coordinates of all the human CD40 ligand amino acids according to Table 1; wherein said computer comprises:

(a) a computer program with instructions to produce said three dimensional representation;

(b) a computer-readable data storage medium comprising a data storage material encoded with computer-readable data, wherein said data comprises the structure coordinates of all the human CD40 ligand amino acids according to Table 1; and

[(b)] (c) a computer screen for displaying said three dimensional representation.

43. (Amended) A computer for producing a three dimensional representation of a binding site for CD40 defined by structure coordinates of human CD40 ligand amino acids Ile127, Ser128, Glu129, Ala130, Ser131, Thr135, Ser136, Ala141, Glu142, Lys143, Gly144, Tyr145, Tyr146, Cys178, Asn180, Ser185, Gln186, Ala187, Pro188, Ile190, Ala191, Ser192, Ser197, Pro198, Gly199, Arg200, Phe201, Glu202, Arg203, Ile204, Arg207, Ala209, Thr211, Pro217, Cys218, Gly219, Gln220, Glu230, Leu231, Gln232, Asn240, Val241, Thr242, Asp243, Ser245, Val247, Ser248, His249, Gly250, Thr251, Gly252 and Phe253, which correspond to residues 12, 13, 14, 15, 16, 20, 21, 26, 27, 28, 29, 30, 31, 63, 65, 70, 71, 72, 73, 75, 76, 77, 82, 83, 84, 85, 86, 87, 88, 89, 92, 94, 96, 102, 103, 104, 105, 115, 116, 117, 125, 126, 127, 128, 130, 132, 133, 134, 135, 136, 137, and 138, respectively, of SEQ ID NO: 3, according to Table 1;

wherein said computer comprises:

(a) a computer program with instructions to produce said three dimensional representation;

(b) a computer-readable data storage medium comprising a data storage material encoded with computer-readable data, wherein said data comprises the

structure coordinates of human CD40 ligand amino acids Ile127, Ser128, Glu129, Ala130, Ser131, Thr135, Ser136, Ala141, Glu142, Lys143, Gly144, Tyr145, Tyr146, Cys178, Asn180, Ser185, Gln186, Ala187, Pro188, Ile190, Ala191, Ser192, Ser197, Pro198, Gly199, Arg200, Phe201, Glu202, Arg203, Ile204, Arg207, Ala209, Thr211, Pro217, Cys218, Gly219, Gln220, Glu230, Leu231, Gln232, Asn240, Val241, Thr242, Asp243, Ser245, Val247, Ser248, His249, Gly250, Thr251, Gly252 and Phe253, which correspond to residues 12, 13, 14, 15, 16, 20, 21, 26, 27, 28, 29, 30, 31, 63, 65, 70, 71, 72, 73, 75, 76, 77, 82, 83, 84, 85, 86, 87, 88, 89, 92, 94, 96, 102, 103, 104, 105, 115, 116, 117, 125, 126, 127, 128, 130, 132, 133, 134, 135, 136, 137, and 138, respectively, of SEQ ID NO: 3, according to Table 1; and

[b)] (c) a computer screen for displaying said three dimensional representation.